REMARKS

Claims 1, 4-8, 11, 14, 18-21, 24, 27-30, 32-33, and 35-37 are currently pending. Claims 2-3, 9-10, 12-13, 15-18, 22-23, 25-27, and 31-34 have been canceled. Claims 1, 14, 24, 28, and 35-37 are currently amended. Support for the claim amendments and new claims may be found throughout the specification and claims as originally filed, including, for example, in the specification as published (U.S. Publication No. 2004/0259101) original claims 18, 27, and 33 and in the specification in paragraphs [0007], [0013], [0015], [0017], [0027], [0037]-[0038], [0045]-[0051], [0066]-[0068] (Example 2), and [0070]-[0072] (Example 3). Applicant believes that no new matter is presented by the amendment.

Amendment of the originally filed claims, or cancellation of any claims should in no way be construed as an acquiescence, narrowing, or surrender of any subject matter. The amendments are being made not only to point out with particularity and to claim the present invention, but also to expedite prosecution of the present application.

Rejections under 35 U.S.C. § 112, First Paragraph

The Office rejected claims 14, 18-21, 24, 27-30, 33, and 36-37 under 35 U.S.C. § 112, first paragraph alleging failure to comply with the enablement requirement. In particular, the Office states, on page 6 of the instant Action, that the method is not enabled "because it has not been shown that just any 'positive' result from just any addition[al] assay would predictably indicate that a patient has colorectal cancer or has abnormal proliferating colorectal cancer cells." Applicant respectfully traverses the rejection.

Without acquiescing to the Office's position, Applicant has amended independent claims 14 and 24 to recite that the "at least one additional assay" is selected from the group consisting of a DNA integrity assay, mutation detection, enumerated loss of heterozygosity (LOH), expression assays, and fluorescent in situ hybridization (FISH). Claims 18, 27, and 33 have been canceled. Claims 19-21 and 36 depend from claim 14, and claims 28-30 and 37 depend from claim 24. Support for the claim amendments may be found in original claims 18 and 27 and in the specification as published in paragraphs [0013], [0015], [0017], [0037]-[0038], [0045]-[0051], [0066]-[0068] (Example 2), and [0070]-[0072] (Example 3). No new matter has been added.

Applicant believes that the amendment to claims 14 and 24 obviates the rejection. Accordingly, Applicant respectfully requests withdrawal of this rejection.

Rejections under 35 U.S.C. § 103

The Office rejected claims 1, 4, 7, 11, 14, 20, 24, 29, 33, and 35-37 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Loktionov *et al.* (Clinical Research, 1998, 4:337-342) in view of Hromadnikova *et al.* (BMC Pregnancy and Childbirth, 2002, 2:1-5). Applicant respectfully traverses the rejection.

The Office, on page 8 of the instant Action, asserts, "Loktionov *et al.* teaches a method of diagnosing and screening a patient for the presence of colorectal cancer comprising measuring quantitative amounts of patient genomic DNA in a stool sample comprising shed cells or shed debris wherein the quantitative amounts are measured by measuring amounts of fragments of less than 200 bp." Applicant respectfully disagrees. Loktionov *et al.* does not disclose measuring genomic DNA from a stool sample comprising shed cells and shed cellular debris, where such DNA may be substantially degraded. Rather, the method disclosed in Loktionov *et al.* teach measuring an amount of DNA extracted from whole cells. Specifically, Loktionov *et al.* teach isolating exfoliated colonocytes using magnetic beads coated with epithelium-specific antibodies and washing the whole cells before cell lysis, DNA extraction, and quantitation. Loktionov *et al.* does not disclose or suggest isolating DNA from shed cellular debris from the stool sample.

The Office, on page 11 of the instant Action, asserts that Loktionov *et al.* teach isolating DNA from cellular debris because the isolated whole coloncytes are lysed in an lysis buffer. Cellular debris arising from exfoliated whole cells following experimental cell lysis is distinct from shed cellular debris that is present in a stool sample as a result of natural processes, including, for example, apoptosis. Without acquiescing to the Office's position, Applicant has amended independent claims 1, 14, and 24 to recite "determining a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells and shed cellular debris." Support for the claim amendments may be found throughout the specification as published including paragraphs [0007] and [0027]. No new matter is added.

In determining a quantitative amount of genome equivalents of patient genomic DNA in a stool sample, the present invention requires that the stool sample comprises shed cells and shed cellular debris. Thus, the present invention is determining a quantitative amount of genome equivalents of patient genomic DNA in a stool sample from both the DNA contained within intact exfoliated cells and substantially degraded DNA contained within shed cellular debris. The instant specification states in paragraph [0007]:

> According to the invention, tissue or bodily fluid samples, especially those described below, contain shed cellular debris. In diseases[,] such as cancer[,] in which cells undergo uncontrolled cell growth and the cell cycle mechanisms are destroyed or impaired, it is believed . . . that the samples containing cellular debris from such patients have an increased amount of nucleic acid relative to samples from certain healthy patients.

The instant specification also states in paragraph [0038]:

> DNA obtained from exfoliated normal cells (i.e., noncancerous cells) is different than DNA obtained from exfoliated cancer or precancer cells because normal exfoliated cells typically have undergone apoptosis, and thus, produce cellular debris comprising DNA that has been substantially degraded.

Because Loktionov's method isolates whole cells prior to cell lysis it selects only a subpopulation of the DNA that is present in the stool sample. As such, Loktionov's method does not isolate shed cellular debris that is naturally present in the stool sample. Therefore, Loktionov's method cannot be used for determining a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells and shed cellular debris.

In addition, Loktionov *et al.* does not teach or disclose determining genome equivalents of patient genomic DNA by measuring an amount of nucleic acid fragments, said fragments having length of 200 bp or less. Loktionov *et al.* teach determining an amount of nucleic acid by measuring an absorbance measurement at 260 and 280 nm. Such an absorbance measurement cannot discriminate DNA fragments based on size. However, the Office asserts on page 11 of the instant Action that "the instant claims are not drawn to methods of discriminating DNA fragments based on size." Without acquiescing to the Office's position, Applicants have amended claims 1, 14, and 24 to recite "measuring an amount of amplified nucleic acid fragments, said fragments having length of 200 bp or less." No new matter is added.

The Office has also asserted that "Loktionov *et al.* teach a method comprising using PCR to detect an amount of 113 bp fragment of patient genomic DNA in a stool sample comprising shed cells or shed debris to confirm DNA quality in order to identify a patient as a candidate for additional cancer testing if the amount is above a predetermined threshold amount, which would indicate a positive screen . . . ." Applicant respectfully disagrees. As discussed above, Loktionov does not teach isolating DNA from shed cellular debris. Moreover, Loktionov does not teach or suggest that detection of a 113 bp fragment was used to identify a patient as a candidate for additional testing. Rather, Loktionov *et al.* state on page 338, right column:

> DNA concentrations were determined by absorbance measurement at 260 and 280 nm using a CE 2041S spectrophotometer . . . . Results were calculated for overall amount of DNA per stool sample and expressed as SDNAI or amount of DNA (ng) isolated per gram of stool. PCR amplification of a 113-bp fragment of *k-ras* gene exon 1 region was performed using sense primer . . . and antisense primer . . . as previously described . . . to confirm quality of extracted DNA.

Thus, Loktionov bases it stool DNA index on DNA isolated from whole cells and absorbance measurements at 260 and 280 nm.

Further, the Office, on page 9 of the instant Action, states that while "Loktionov *et al.* does not specifically teach genomic DNA amounts expressed in terms of 'genome equivalents' or that the PCR method is 'quantitative PCR'," that these deficiencies are made up in the teachings of Hromadnikova *et al.* Applicant respectfully traverses the rejection. Hromadnikova *et al.*, does not cure the deficiencies of Loktionov *et al.* because neither reference teaches nor suggests determining a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells and shed cellular debris. Moreover, it was unexpected that measuring nucleic acid fragments of length less than 200 base pairs could distinguish healthy patients from those that should undergo additional cancer testing. Determining a quantitative amount of genome equivalents of genomic DNA in a stool sample comprising shed cells and shed cellular debris by measuring an amount of nucleic acid fragments, said fragments having length of 200 bp or less, surprisingly provides an accurate measurement because it is indicative of the total amount of DNA that is present in a stool sample of both healthy individuals and cancer patients. Thus, the quantitative amount of genome equivalents of genomic DNA in a

stool sample comprising shed cells and shed cellular debris can be discriminatory between healthy individuals and patients requiring additional cancer testing.

Accordingly, withdrawal of this rejection is respectfully requested.

The Office rejected claims 1, 4-8, 11, 14, 18-21, 24, 27-30, 33, and 35-37 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Loktionov *et al.* (Clinical Research, 1998, 4:337-342) in view of Hromadnikova *et al.* (BMC Pregnancy and Childbirth, 2002, 2:1-5) and further in view of Ahlquist *et al.* (Gastroenterology, 2000, 119:1219-1227).

The Office, on page 13 of the instant Action states:

> The combined teachings of Loktionov *et al.* and Hromadnikova et al. do not specifically teach methods of detecting the presence of abnormal proliferating colorectal cancer cells/detecting colorectal cancer/diagnosing colorectal cancer by: (1) performing a DNA integrity assay; (2) detecting a ras mutation, or (3) performing a colonoscopy. However, these deficiencies are rendered obvious or made up in the teachings of Ahlquist *et al.*

Applicant respectfully traverses the rejection. None of Loktionov *et al.*, Ahlquist *et al.*, or Hromadnikova *et al.* teach or suggest determining a quantitative amount of genome equivalents of patient genomic DNA in a stool sample comprising shed cells and shed cellular debris, wherein the quantitative amount of genome equivalents is determined by measuring an amount of amplified nucleic acid fragments, said fragments having length of 200 bp or less, as recited in claims 1, 14, and 24.

Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicant respectfully requests reconsideration of the rejections and Applicant request allowance of pending claims 1, 4-8, 11, 14, 19-21, 24, 28-30, and 35-37 in due course. The Examiner is cordially invited to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance, or if there are any questions regarding this case.

Respectfully submitted,

Date: August 28, 2008
Reg. No. 57,961

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